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Phase I Dose-Escalation Study of the Anti-CD70 Antibody ARGX-110 in Advanced Malignancies

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Abstract

Purpose: The purpose of this study was to evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary antitumor efficacy of ARGX-110, a glyco-engineered monoclonal antibody, targeting CD70, in patients with CD70 expressing advanced malignancies.

Experimental Design: Dose escalation with a sequential 3+3 design was performed in five steps at the 0.1, 1, 2, 5, and 10 mg/kg dose levels ($N = 26$). ARGX-110 was administered intravenously every 3 weeks until progression or intolerable toxicity. Dose-limiting toxicity was evaluated in the 21 days following the first ARGX-110 administration (Cycle 1). Samples for pharmacokinetics and pharmacodynamics were collected.

Results: Dose-limiting toxicity was not observed and the maximum tolerated dose was not reached. ARGX-110 was generally well tolerated, with no dose-related increase in treatment-emergent adverse events (TEAE). The most common TEAE were fatigue and drug related infusion-related reactions (IRR). Of the 20 SAEs reported, five events, all IRRs, were considered related to ARGX-110. ARGX-110 demonstrates dose proportionality over the dose range 1 to 10 mg/kg, but not at 0.1 mg/kg and a terminal half-life of 10 to 13 days. The best overall response was stable disease (14/26) in all 26 evaluable patients with various malignancies and the mean duration of treatment was 15 weeks. No dose–response related antitumor activity was observed, but biomarker readouts provided signs of biological activity, particularly in patients with hematologic malignancies.

Conclusions: This dose-escalation phase I trial provides evidence of good tolerability of ARGX-110, pharmacokinetics, and preliminary antitumor activity at all dose levels in generally heavily pretreated patients with advanced CD70-positive malignancies. *Clin Cancer Res; 23(21); 6411–20. ©2017 AACR.*

Introduction

With only limited expression in normal tissues, CD70 is an increasingly recognized target for the development of antibody-based therapies (1–4). CD70, a member of the tumor necrosis factor receptor ligand family, is transiently expressed on activated B and T cells, and mature dendritic cells (5–9). It interacts with its receptor CD27 that is more widely expressed on various subsets of B and T cells, and on a subset of natural killer (NK) cells. CD70-mediated effects are generally based on activation of CD27-associated signaling pathways. CD27 activation results in enhanced activity of NF-κB and Jun amino-terminal kinase (JNK) pathways, which have been implicated in differentiation, activation, and survival of B and T cells (2, 8, 10–13). Upon binding of CD70 to CD27, a soluble form of CD27 (sCD27) is released. High sCD27 levels have been detected in patients with autoimmune disease and cancer. Chronic expression of CD70 leads to lethal immune suppression in mice (7), and to exhaustion of effector memory T cells in B-NHL (14).

CD70 is strongly expressed in a large spectrum of solid tumors and hematologic malignancies, such as renal, pancreatic, lung, ovarian carcinomas, and lymphomas (1, 15–17). Although CD70–CD27 signaling in the immune system can lead to induction of both immunity and tolerance, its roles in the microenvironment of various tumors are less clear (2, 8, 9). Initially, CD70 expression on solid tumors was believed to be an epiphenomenon of tumor biology. Recent evidence suggests that it may also play a role in the evasion of immune surveillance by malignant cells as observed for programmed death-1 (PD1) and its ligand (PD-L1), which are frequently upregulated by a range of tumor types (18). Interestingly, tumor cells expressing CD70 increase the frequency of T-regulatory cells (Tregs) and activate them in the tumor microenvironment, thereby creating an immunosuppressive microenvironment (19–21). In addition, in some tumors like B-cell malignancies, CD70 is co- and overexpressed with its receptor CD27, leading to autocrine-paracrine signaling of the tumor cells and resulting in its survival and proliferation (13, 22). Targeting CD70 may therefore be associated with a clinically beneficial therapeutic index.

ARGX-110 is a next-generation germlined (reverse mutation to human germline sequences) mAb that binds to human CD70

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Translational Relevance

With only limited expression in normal tissues and strong expression on tumor cells, CD70 is an attractive target for antibody-based therapy. This report describes the first-in-human experience of ARGX-110 in patients with advanced solid tumors and hematologic malignancies expressing CD70. Glyco-engineered ARGX-110 blocks CD70–CD27 signaling, which is thought to inhibit evasion of tumor immune surveillance as well as inhibiting tumor cell proliferation and survival, whereas its effector functions being complement-dependent cytotoxicity (CDC), antibody dependent cellular phagocytosis (ADCP), and enhanced ADCC efficiently kill CD70-expressing tumor cells. No DLTs were observed and no MTD was reached. Stable disease with mean duration of 3.7 months was observed in 53.8% of the generally heavily pretreated patients and mean duration of treatment was 15 weeks. Biomarker readouts provided signs of biological activity, particularly in patients with hematologic malignancies. These results support the continued clinical development of ARGX-110 in various tumor types.

with picomolar affinity and blocks CD70–CD27 signaling (23). It has been modified by afucosylation of the Fc region to induce enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) using POTELLIGENT technology (24, 25), to provide a potent mAb for use in cancer therapy. ARGX-110 has multiple mechanisms of action, including blocking CD70–CD27 signaling, which is thought to inhibit evasion of tumor immune surveillance by reducing the number of Tregs in the tumor microenvironment as well as to inhibit tumor proliferation and survival, whereas its effector functions being complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), and the enhanced ADCC are responsible for the efficient killing of CD70-expressing tumor cells (23).

We report results from a first-in-human multicenter phase I study of ARGX-110 in generally heavily pretreated patients with advanced solid tumors and hematologic malignancies that express the CD70 antigen. This study evaluated the safety, pharmacokinetics, pharmacodynamics, and preliminary antitumor efficacy.

Population and Methods

Patients and study design

The study was an open-label, non-randomized, multicenter study. The primary objective was to determine the maximum-tolerated dose (MTD) and establish the recommended phase II dose (RP2D) of ARGX-110 and the secondary objectives were to investigate pharmacokinetics (PK), biomarkers of drug activity, and preliminary evidence of antitumor efficacy.

The trial (*EudraCT* number 2012-005046-38) was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices Guidelines. The clinical study protocol and its amendments, informed consent documents, and any other appropriate study-related documents were reviewed and approved by the applicable regional review boards or ethic committees. All authors had access to the primary clinical data.

Patients of $\geq$18 years of age with solid tumor or lymphoma positive for the CD70 antigen in archived or fresh tumor tissue, as determined by immunohistochemistry (>10%) or fluorescent-activated cell sorting (FACS) for leukemia, were eligible. The malignancy had to be refractory to or relapsing after standard therapy (including autologous stem cell transplantation, ASCT). Additional eligible and exclusion criteria are described in Supplementary Methods.

Treatment and rationale for dose selection

The starting dose (0.1 mg/kg) was lower than the human equivalent dose (HED) at 9.7 mg/kg calculated from the no-observed-adverse-effect level (NOAEL) determined in cynomolgus monkeys (30 mg/kg). It was predicted to result in a human AUC approximately 700-fold lower than the AUC associated with the NOAEL.

The dose-escalation phase used a sequential 3+3 design for determination of MTD. The recommended phase II dose was the dose level below the MTD if reached. Patients received ARGX-110 at doses of 0.1, 1, 2, 5, and 10 mg/kg once every 3 weeks (on day 1 of a 21-day cycle) until they developed progressive disease (PD) or intolerable drug-related toxicity, or withdrew consent.

For the first dose cohort of 0.1 mg/kg, the first two patients who received ARGX-110 experienced IRRs during their first infusion. This led to the introduction of pre-medication to minimize the risk of IRRs in a protocol amendment. Premedications were administered before each intravenous administration of ARGX-110 included acetaminophen (1,000 mg) and antihistamine (diphenhydramine 50 mg equivalent) was taken orally 12 and 0.5 hours before infusion, and IV glucocorticoid (hydrocortisone 100 mg equivalent) 0.5 hour before infusion. Variance based on institutional practice was acceptable once discussed with the sponsor.

Safety

Patients were hospitalized to receive the first dose of ARGX-110 and observed for the development of adverse events (AE) according to institutional practice for a minimum of 24 hours. Doses in later cycles were administered in the outpatient setting. After the first ARGX-110 administration at each dose level, patients were observed for signs of toxicity for $\geq$24 hours before discharge; the observation period was $\geq$4 hours after all other doses. At each dose level, patients were evaluated for toxicity during treatment and at 30 and 60 days after the last ARGX-110 infusion. All AEs were followed up until resolution or 60 days from the last dose of ARGX-110.

Dose-limiting toxicities (DLT) were defined as drug-related grade 3 or 4 clinical AEs, severity graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 4.03, occurring 21 days (cycle 1) following the first ARGX-110 administration (except inadequately treated nausea/vomiting). Grade 3 thrombocytopenia without hemorrhage, grade 3 neutropenia without fever, and grade 4 neutropenia lasting 7 days or less did not qualify as a DLT. For acute infusion reaction or cytokine release syndrome, a DLT was defined as grade 4 drug-related toxicity or grade 3 that could not be resolved by infusion-rate reduction or interruption, or supportive care.

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Assessments

A full clinical history and clinical and biological evaluation, including blood counts, differential serum chemistry, renal, and hepatic function measurement, was carried out. Serum samples were collected from all patients pre-administration cycle 1, day 1 (C1D1), and then on days 2, 8, and 15 after administration of the first dose of cycle 1, pre- and post-dose for subsequent cycles, and at the 30- and 60-day follow-up (FU30 and FU60, respectively) visits to determine serum concentrations of ARGX-110 using a validated ELISA.

Exploratory pharmacodynamic (PD) markers were investigated for ARGX-110 modes of action. CD70 qPCR was performed on cDNA [optimal blend of oligo(dT) and random primers, Bio-Rad] prepared from RNA extracted from whole blood collected at pre-C1, 2 and 6 hours post-C1, and then pre-C2 and 2 hours post-C2 and later cycles (Biogazelle Zwijnaarde). Soluble CD27 (sCD27) in serum (pre- and post-administration C1 and then only pre-dose) was measured using the PeliKine compact human sCD27 ELISA (Sanquin). A complement activation assay was used to investigate ability to induce CDC at the same timepoints as sCD27 samples (23). NK cells were counted (BD Biosciences TrueCount $CD45^+CD3^-CD16^+CD56^+$ lymphocytes). B and T lymphocytes subsets (TriTest CD3/CD19/CD45, BD Biosciences) and regulatory T cells (Treg, detected by CD45, CD4, CD25, CD127, CD27, and the intracellular Foxp3) was investigated by flow cytometry in whole blood pre-treatment for all cycles and follow up (FU30 and FU60 days).

All patients who had completed one cycle of therapy and undergone at least one scheduled tumor assessment were considered evaluable for response by the investigators. Tumor response was recorded as the best response achieved (expressed as % of baseline measurement) for all patients. Patients with solid tumors were evaluated for response according to RECIST (26) or the immune-related RECIST (ir-RECIST; ref. 27). Patients with hematologic malignancies were assessed according to disease-specific response evaluation scheme [e.g., Cheson criteria (28), mSWAT (29)].

Statistical methods

Continuous variables are summarized by descriptive statistics: number of patients (*N*), mean, standard deviation (SD), minimum, median, and maximum values. Geometric mean and coefficient of variation (CV) are presented for PK parameters when appropriate. Categorical data are summarized by absolute and relative frequencies (*n* and %). Statistical analyses were performed using SAS 9.3 or higher or Graphpad prism v. 7.01.

Results

Patient demographics and baseline characteristics

Between 21 February 2013 and 29 December 2014, a total of 26 patients were enrolled and treated in the dose-escalation phase of the study. Initially six patients in the 0.1 mg/kg cohort, five patients in the 1 mg/kg cohort, three patients in the 5 mg/kg cohort, and five patients in the 10 mg/kg cohort were enrolled. The first two patients from the 0.1 mg/kg cohort experienced IRR, which led to the introduction of premedication and one patient was withdrawn prior to cycle 2 for PD. Therefore, three additional patients were included and one additional beyond the 3+3 cohort to allow for investigation of this treatment. A new cohort of 2 mg/kg with seven patients was added to further extend the PK data after enrollment of five patients in the 10 mg/kg cohort.

A total of 26 patients (median age 59.5 years, range 22–78) with advanced malignancies expressing CD70 (22 solid tumors and 3 hematologic malignancies with target positive biopsies and one patient with acute myeloid leukemia (AML), where the malignant cells were CD70 positive by Flow Cytometry, data not shown) were treated with ARGX-110. 53.8% of the patients were male, the majority were Caucasian (92.3%) and 72% had an Eastern Co-operative Oncology Group (ECOG) performance status of 1. Most patients had lived with the diagnosis for one or more years, and had received prior treatment for their malignancy. Table 1 summarizes the characteristics of the patients.

The most common main reason for treatment termination was PD (22/26; 84.6%). Reasons for noncompletion of the study was death (2/26), loss, or refusal to come for follow up (3/26).

Safety and tolerability

Overall, the safety profile of the five dose cohorts during dose escalation was comparable, no DLTs and no MTD were defined.

Treatment emergent AEs (TEAE) were reported in 25 of 26 patients (302 total events) of which the proportion of patients was comparable between dose cohorts. TEAEs reported in 15% of the patients or more (131 events) are listed as preferred term (PT) in Table 2. The most common events were fatigue (17 events in 17/26 patients), infusion-related reactions (IRR; 21 events, all considered related, in 10 patients), dyspnea (11 events in eight patients), and pyrexia (10 events in 8 patients) as shown in Table 2 presented per dose cohort. A total of 79/302 events (26.2%) were considered related to ARGX-110. The most common related event was IRRs (21/79 events in 10 patients out of 26; 38.5%) of which three patients experienced IRR at C1 (two with no premedication at C1), four patients at C2 or C3 only, and three for more than one cycle. IRR symptoms included fever, chills, hypoxia, tremor, nausea, vomiting, hot flashes, anxiety, bronchospasm, dyspnea, and rash. All IRRs were grade 1 to 2.

Among the 131 events that were observed in 15% patients or more, 13 events were grade 3 or 4 (four infections, four anemia, one abdominal pain, three fatigue, and one dyspnea). Three TEAE of grade 3 in the 0.1 mg/kg cohort were drug related as judged by the investigators (hypoxia, decreased appetite, and fatigue). No grade 4 or 5 toxicities were considered related to ARGX-110. Treatment was interrupted in 7/26 patients and 12 AEs in 10 patients led to dose delays between cycles.

Among other more infrequent toxicities, lung infections, or pneumonia were reported in five patients (two grade 3 at 0.1, one grade 3 at 1, and one grade 2 and one grade 3 at 10 mg/kg).

A total of 20 serious adverse events (SAE) in 10/26 patients were recorded. Eight events were reported at 0.1 mg/kg: three IRR events of grade 2 (three patients), two grade 3 pneumonias (two patients), one grade 3 general physical health deterioration, one grade 3 hemolytic anemia, and one grade 1 pyrexia. Five events were reported for two patients at 1 mg/kg: one IRR event of grade 2, one grade 5 respiratory failure, one grade 3 artrial fibrillation, one grade 3 increased blood creatinine, and one grade 3 urinary tract obstruction. One grade 5 general health deterioration event was reported for one patient at 2 mg/kg. No SAE were reported at 5 mg/kg. Finally, six SAEs were reported at 10 mg/kg for two patients: one grade 5 sepsis and two grade 3 edemas (peripheral and scrotal) in one patient, one grade 3 dyspnea, one grade 2 IRR and one grade 2 tibia fracture. Of all SAEs reported, only five

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Table 1. Patient demographics and baseline characteristics

Characteristics		Total ($N = 26$)
Age (years)	Mean (SD)	57.1 (13.03)
	Median [Range]	59.5 [22.0–78.0]
Sex	Male	14 (53.8%)
	Female	12 (46.2%)
Race	Caucasian	24 (92.3%)
	Asian	2 (7.7%)
ECOG	Grade 0	7 (28.0%)
	Grade 1	18 (72.0%)
	Missing	1
Time since cancer diagnosis (years)	<1 year	2 (7.7%)
	>1–5 years	18 (69.2%)
	>5 years	6 (23.1%)
Prior cancer treatments (%)	Chemotherapy	84.2
	Immunotherapy	11.5
	Biological therapy	15.4
	TKI therapy	15.4
	Other targeted therapy	3.8

Abbreviations: *N*, number of patients; TKI, tyrosine kinase inhibitor.

events, all IRRs, were considered related to ARGX-110, all of which resolved during dose escalation.

A total of 7/26 patients (26.9%) died during the study with the majority of them within 3 months after the first dose of ARGX-110 due to disease progression [5/7 patients (71.4%)]. One patient at 1 mg/kg died of respiratory failure and one at 10 mg/kg died from sepsis. Generally, no clear trend could be identified especially for the causes of death or the source of the infections. No death was related to the study treatment as determined by the investigators. Overall, ARGX-110 showed a good safety profile and was well tolerated in all five dose cohorts during dose escalation.

Treatment duration and overall response

All 26 patients were treated with ARGX-110 at cycle 1, with the number of patients (*N*) treated with ARGX-110 decreasing over time. The majority of patients had no dose interruptions (19/26 patients; 73.1%), nor dose delays (16/26 patients; 61.5%). The mean duration of treatment for all 26 patients was 105.9 days (15.1 weeks) as indicated in Fig. 1. The number of cycles ranged from 1 to 23 cycles, with 74.5 weeks until end of treatment (EOT) being the longest for a mesothelioma patient. This was a 50-year-old female, who had two lines of chemotherapy with stable disease (SD) as best response for 6 months before progression, followed by treatment of 10 mg/kg ARGX-110 with SD as best response.

Anti-neoplastic activity was observed at all dose-levels. The best overall response as per investigator review was SD (14/26 patients; 53.8%) as opposed to PD (12/26 patients; 46.2%). The highest percentage of patients with SD was in the 5 mg/kg cohort (3/3 patients; 100.0%). This was followed by a total of 4/6 patients (66.7%) in the 0.1 mg/kg cohort and 3/5 patients (60.0%) in the 1 mg/kg cohort. The 10 mg/kg cohort (2/5 patients; 40.0%) and the 2 mg/kg cohort (2/7 patients; 28.6%) had the lowest number of patients with SD (Fig. 1). Mean duration of SD was 3.7 months.

A 58-year-old female, diagnosed with adenoid cystic parotid carcinoma had lung metastases and PD at the time of enrolment. She had prior left parotidectomy and radiotherapy, but no systemic cancer treatment was done before she received 1 mg/kg ARGX-110. At C3D1 she was stable, which remained until the last cycle 20, when she was progressing and was taken off the study.

A 66-year-old male, diagnosed with papillary renal carcinoma, received treatment at 0.1 mg/kg for 8 cycles before he experienced hemolytic anemia (SAE), which was resolved within 6 weeks. The patient had SD during treatment, but was progressing after treatment interruption and before reentering into the study about 5.5 months later as allowed by the protocol. SD was again recorded at cycle 11 and the patient was maintained in the study until clinical progression after cycle 12.

Assessments and pharmacokinetics

There were no overall trends in the hematology and biochemistry laboratory data over time. Fluctuations were noted, but no clear dose effect was visible. There was no change in the urinalysis parameters.

ARGX-110 demonstrated proportionality over the dose range 1 to 10 mg/kg, but not at 0.1 mg/kg (Fig. 2A). The median C_{max} in cycle 1 was 1.6, 21.6, 39.4, 109.0, and 287.0 μg/mL, for the 0.1, 1, 2, 5, and 10 mg/kg cohorts, respectively and the median AUC was 4072.2, 9036.6, 35845.1, and 72437.8 μg × h/mL for the 1, 2, 5, and 10 mg/kg cohorts, respectively. The median $t_{1/2}$ of ARGX-110

Table 2. Treatment emergent adverse events (TEAE) in ≥15% of patients by preferred term

	ARGX-110 every 3 weeks					
	0.1 mg/kg ($N = 6$)	1 mg/kg ($N = 5$)	2 mg/kg ($N = 7$)	5 mg/kg ($N = 3$)	10 mg/kg ($N = 5$)	Total ($N = 26$)
	n, N	*n, N*	*n, N*	*n, N*	*n, N*	*n, N*
Fatigue	4, 4 (66.7%)	4, 4 (80.0%)	4, 4 (57.1%)	2, 2 (66.7%)	3, 3 (60.0%)	17, 17 (65.4%)
IRR	13, 4 (66.7%)	1, 1 (20.0%)	5, 3 (42.9%)	1, 1 (33.3%)	1, 1 (20.0%)	21, 10 (38.5%)
Dyspnea	3, 2 (33.3%)	1, 1 (20.0%)	1, 1 (14.3%)	3, 2 (66.7%)	3, 2 (40.0%)	11, 8 (30.8%)
Pyrexia	2, 2 (33.3%)	4, 3 (60.0%)	0, 0	1, 1 (33.3%)	3, 2 (40.0%)	10, 8 (30.8%)
Decreased appetite	4, 2 (33.3%)	0, 0	4, 3 (42.9%)	2, 2 (66.7%)	0, 0	10, 7 (26.9%)
Abdominal pain	5, 3 (50.0%)	2, 2 (40.0%)	0, 0	1, 1 (33.3%)	0, 0	8, 6 (23.1%)
Nausea	1, 1 (16.7%)	2, 2 (40.0%)	1, 1 (14.3%)	2, 1 (33.3%)	1, 1 (20.0%)	7, 6 (23.1%)
Anemia	3, 3 (50.0%)	2, 1 (20.0%)	1, 1 (14.3%)	0, 0	1, 1 (20.0%)	7, 6 (23.1%)
Diarrhea	1, 1 (16.7%)	5, 3 (60.0%)	0, 0	0, 0	1, 1 (20.0%)	7, 5 (19.2%)
Headache	3, 2 (33.3%)	2, 2 (40.0%)	0, 0	1, 1 (33.3%)	0, 0	6, 5 (19.2%)
Edema peripheral	3, 3 (50.0%)	0, 0	0, 0	1, 1 (33.3%)	1, 1 (20.0%)	5, 5 (19.2%)
Cough	1, 1 (16.7%)	1, 1 (20.0%)	2, 2 (28.6%)	1, 1 (33.3%)	0, 0	5, 5 (19.2%)
Back pain	3, 2 (33.3%)	1, 1 (20.0%)	0, 0	1, 1 (33.3%)	0, 0	5, 4 (15.4%)
Myalgia	3, 3 (50.0%)	0, 0	0, 0	1, 1 (33.3%)	0, 0	4, 4 (15.4%)
General physical deterioration	2, 2 (33.3%)	1, 1 (20.0%)	1, 1 (14.3%)	0, 0	0, 0	4, 4 (15.4%)
Nasopharyngitis	0, 0	2, 2 (40.0%)	1, 1 (14.3%)	0, 0	1, 1 (20.0%)	4, 4 (15.4%)

Abbreviations: *n*, number of events; *N*, number of patients; %, percentage of patients.

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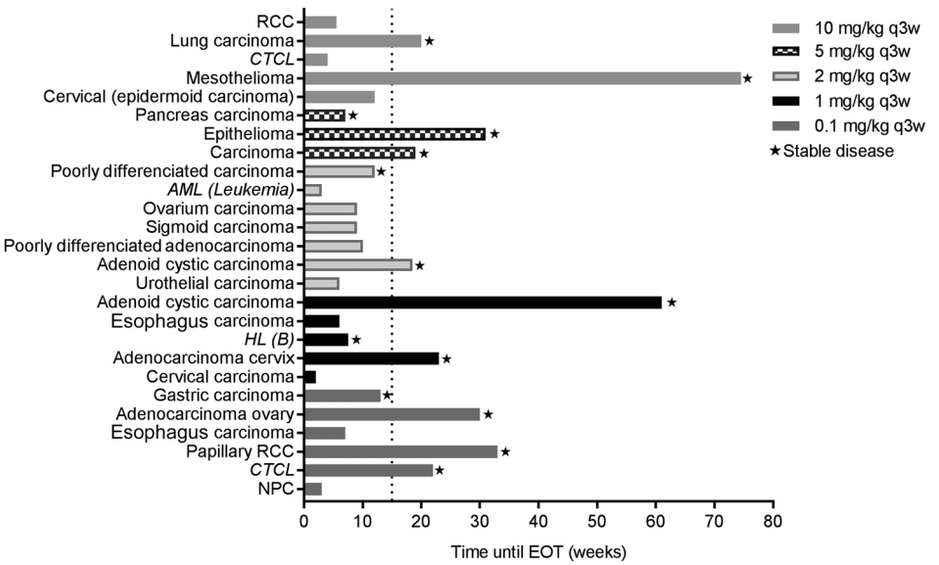

Figure 1.

Efficacy outcome. Anti-neoplastic outcomes (compared to baseline assessments) by investigator review for patients that completed at least one cycle of therapy and had undergone at least one tumor assessment. Each bar represents one patient and the length of the bar the duration (weeks) of treatment until EOT. Patients are grouped after dose. Patients with SD as best response are indicated with a star, whereas patients with PD are without symbol. Hematologic malignancies are in italics. The vertical dotted line indicates the mean duration of treatment (weeks). RCC, renal cell carcinoma; HL (B), Hodgkin's lymphoma, B-cell; NPC, nasopharyngeal cancer; CTCL, cutaneous T cell lymphoma; AML, acute myeloid leukemia.

ranged from 208.7 hours for the 1 mg/kg to 315.3 hours for the 10 mg/kg cohort (8.7–13.1 days; Table 3 and Fig. 2B). Except for C_{max}, calculations could not be appropriately interpreted due to the sensitivity of the bioanalytical assay not permitting measurement of concentrations of ARGX-110 after the 24-hour time point in the 0.1 mg/kg dose group [lower limit of quantification (LLOQ) 0.5 μg/mL]. As a result, the terminal elimination phase is not well characterized for that dose and $t_{1/2}$ cannot be estimated (and thus also not CL, V_d, and AUC_∞). The data should be carefully interpreted because of the limited number of patients and short observation window. There were no apparent correlations between pharmacokinetic parameters and either clinical treatment response or adverse events.

CDC was measured by blood sampling predose and 2 hours after the first administration of ARGX-110 for all cohorts. The serum (containing ARGX-110) was incubated with ($CD70^+$) U266 cells that are sensitive to CDC and the amount of lysis was measured by flow cytometry. Analysis of CDC and C_{trough} at pre-C2 (480 hours) in serum at the same time-point shows that there was complete lysis by CDC at all doses even before the next dose (mean C_{trough} for dose group 1 mg/kg was 2.4 μg/mL), except for 0.1 mg/kg cohort, where CDC was only observed 2 hours after the first dose (Fig. 2C). This correlates well with the serum concentrations of ARGX-110 (Fig. 2B), indicating that for maximal CDC lysis, a serum concentration of more than 1.6 μg/mL was needed.

The read out of the biomarkers gave some insight in the mechanisms of action of the drug. Target modulation in circulating normal lymphocytes and tumor cells were followed by measuring CD70 mRNA levels using qPCR. There was an overall tendency for decreased CD70 mRNA levels after treatment compared to pre-dose (Fig. 2D). One cutaneous T-cell lymphoma (CTCL) patient with Sézary syndrome in the 10 mg/kg cohort showed the highest levels of CD70 measured by qPCR (31 CNTQ vs. mean around 3 CNTQ for the rest of the patients) with depletion by 77% already 2 hours after the first dose and remained low until 2 hours after the second ARGX-110 administration (Fig. 2E). Unfortunately, the patient was off the study due to non-drug related sepsis after two doses. This patient also had high levels of sCD27 (>1,000 IU/mL) indicating a high tumor burden, but it remained unchanged after ARGX-110 administration. Overall, the mean sCD27 levels at baseline were not significantly increased compared to healthy levels (200–500 U, in-house data) in all cohorts and there was no major change during treatment.

The mean of regulatory T cells (Tregs) versus $CD4^+$ cell numbers in whole blood were not altered as shown for pre-treatment samples C1–C3 when >50% of the patients were still in the study (Fig. 3A) except for a 22-year-old patient diagnosed with Hodgkin's lymphoma (HL), who entered the study with strong CD70 expression but no coexpression of CD27 (data not shown). The patient had three lines of previous chemotherapy and ASCT followed by lenalidomide. Before treatment with 1 mg/kg of ARGX-110, high numbers of Tregs could be detected in the blood (12.7% of total number of $CD4^+$ T lymphocytes). The frequency dropped to almost normal levels (6% vs. 4% as found in healthy individuals) after four treatment cycles. After the patient was taken off the study, the analysis of two additional blood samples taken in the follow up period (FU) 52 (FU30) and 73 (FU60) days after the last treatment cycle revealed a rise in circulating Tregs (10% of total number of $CD4^+$ T cells) whereas the patient did not receive any treatment at the time (Fig. 3B).

A similar observation was made in one AML patient, who also had high numbers of circulating Tregs prior to treatment (13%), which came down after a single administration of ARGX-110 at a dose of 2 mg/kg (9%, data not shown).

As per investigator information, a 78-year-old female diagnosed with stage IIb CTCL in 1997, had a detectable $CD3^+$/$CD4^-$/$CD8^-$ TCRγδ malignant clone (12%) in the circulation and skin lesions on one arm and one leg before enrolment. She was treated with 0.1 mg/kg ARGX-110 for six cycles and her skin lesions remained stable, but the circulating malignant clone was not detectable upon the first measurement at cycle 4, which was confirmed again 1 month later, indicating a complete response in the blood compartment according to the mSWAT score (29). The patient withdrew consent for personal reasons.

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No major changes in percentage of $CD3^+$ T cells or $CD19^+$ B cells of total $CD45^+$ lymphocytes were observed in any of the cohorts (Fig. 3C and D). For all cohorts, the mean NK cell counts (Fig. 3E) were not affected during the treatment for any of the cohorts.

Discussion

In the dose escalation phase of this phase I study of ARGX-110 in patients with solid tumors and hematologic malignancies, neither DLT nor MTD were observed across ARGX-110

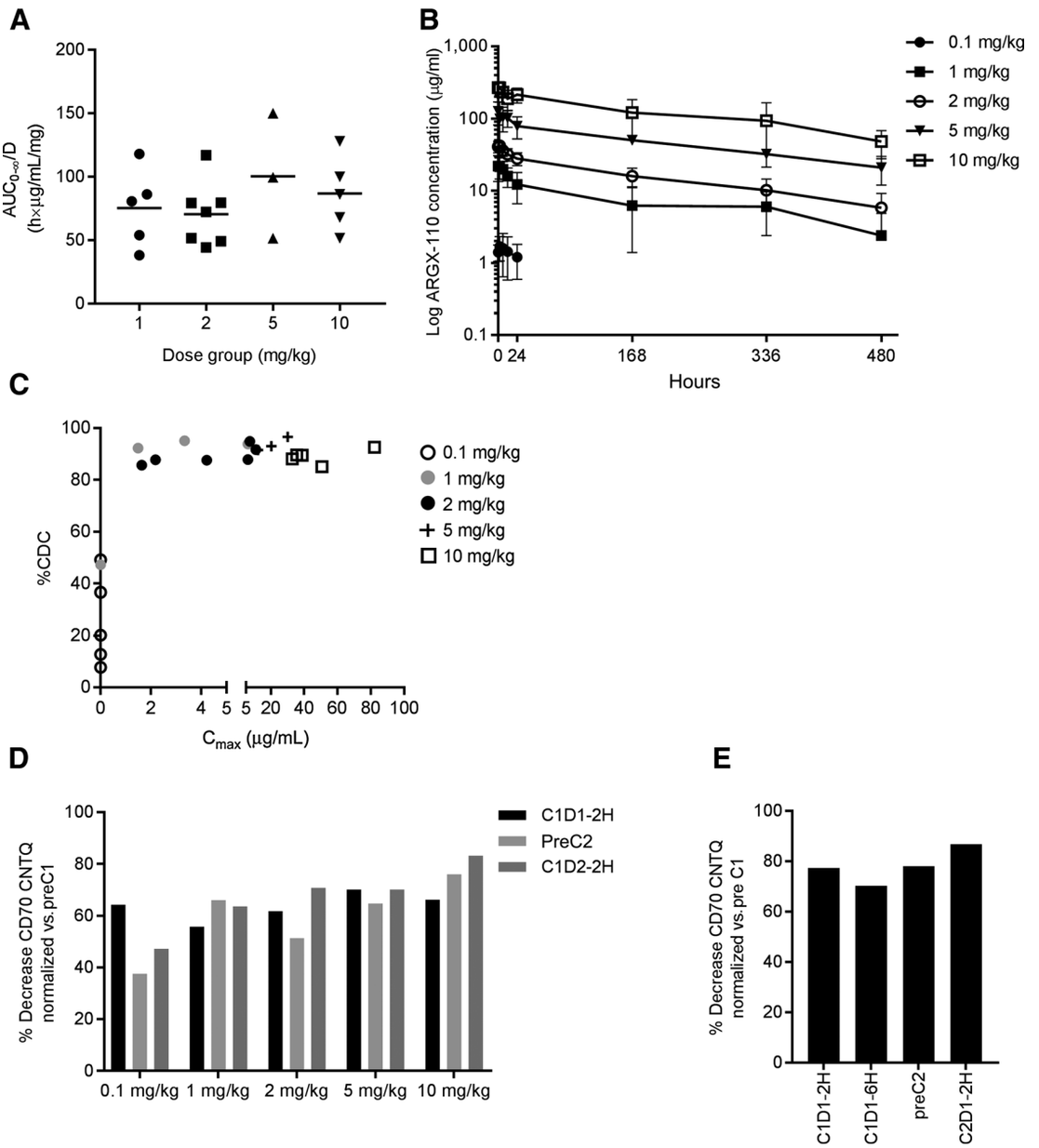

Figure 2.

Pharmacokinetics of ARGX-110 and exploratory pharmacodynamics. **A,** Dose proportionality for dose normalized $AUC_{0-\infty}/D$ (h × µg/mL/mg) for dose groups 1 to 10 mg/kg. **B,** Serum concentrations of ARGX-110 after one administration measured by ELISA on immobilized CD70 for samples at each dose level. Data are presented as arithmetic mean (µg/mL) and standard error (SD) on a linear-log scale at the different time points (hours). **C,** CDC (% lysis) in peripheral blood samples for each dose level (0.1, 1, 2, 5, and 10 mg/kg) at 480 hours (pre-C2 on day 21) plotted against the C_{trough} (µg/mL) in serum at the same time-point. Dotted line indicate effective dose 1.6 µg/mL. **D,** Target modulation in circulating normal lymphocytes and tumor cells was followed by measuring CD70 mRNA levels using qPCR. Expressed as % change from baseline (pre-C1) after normalization (mean of triplicates) at dose levels 0.1, 1, 2, 5, and 10 mg/kg. **E,** Target modulation of circulating clone measured by CD70 mRNA using qPCR in a CTCL patient treated at 10 mg/kg for two cycles as % decrease normalized versus baseline (pre-C1), 2 hours post-C1 (C1D1-2H), 6 hours post C1 (C1D1-6H), pre-C2 and 2 hours post-C2 (C2D1-2H). Expressed as % decrease from baseline (pre-C1) after normalization (mean of triplicates).

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Table 3. Pharmacokinetics of ARGX-110 at cycle 1 (21 days after the first ARGX-110 administration)

		0.1 mg/kg (*N* = 6)	1 mg/kg (*N* = 5)	2 mg/kg (*N* = 7)	5 mg/kg (*N* = 3)	10 mg/kg (*N* = 5)
C_{max} (μg/mL)	*N*	6	5	7	3	5
	GM	1.78	22.5	42.6	123.8	288.4
	%CV	44.1	32.6	15.6	33.3	13.5
	Median	1.61	21.6	39.4	109	287
Terminal rate constant	*N*	0	5	7	3	5
($hours^{-1}$)	GM	NA	0.003	0.003	0.002	0.002
	%CV	NA	39.7	49.7	36.1	26.7
	Median	NA	0.003	0.003	0.002	0.000
AUC_{∞} (μg × h/mL)	*N*	0	5	7	3	5
	GM	NA	4072.2	9036.3	35845.1	72437.8
	%CV	NA	58.7	41.5	16.4	45.4
	Median	NA	4959.3	9409.6	32812.0	68095.5
CL (mL/h)	*N*	0	5	7	3	5
	GM	NA	15.9	15.0	9.7	11.7
	%CV	NA	53.3	36.9	35.9	34.1
	Median	NA	12.5	13.7	10.1	11.5
V_d (L)	*N*	0	5	7	3	5
	GM	NA	4.8	4.8	4.9	4.9
	%CV	NA	21.0	22.6	38.5	37.2
	Median	NA	4.9	4.6	4.6	4.2
$t_{1/2}$ (h)	*N*	0	5	7	3	5
	GM	NA	208.7	219.9	351.2	291.4
	%CV	NA	34.0	45.7	33.6	24.8
	Median	NA	263.1	246.7	368.8	315.3

Abbreviations: AUC_{∞}, area under the serum concentration–time curve from time 0 to ∞; C_{max}, maximum concentration; CL, clearance; CV, confidence of variation; GM, geometric mean; *N*, number of patients; NA, not applicable since the values are below lower limits of quantification (BLLOQ) at Day 7 (168 hours); $t_{1/2}$, half-life; V_d, apparent volume of distribution.

doses of 0.1 to 10 mg/kg, which has been observed in trials involving immune targeting antibodies (reviewed by ref. 30). No dose–response was observed in terms of anti-neoplastic efficacy or toxicity and the best overall response was SD, observed in more than half of the patients (53.8%) and mean duration of treatment was 15 weeks, corresponding to five cycles every 3 weeks. The mean duration of SD was 3.7 months with the longest 14 months.

ARGX-110 was generally well tolerated, and most events were mild or moderate and easily managed. There were no major hematologic effects and no effect on the total number of B-, T-, or NK cells as shown by flow cytometry. Fatigue was the most common TEAE, followed by IRRs (in 38.5% of patients), which were observed at all doses and different cycles between C1 and C3. Two patients, who received 0.1 mg/kg ARGX-110 before premedication, experienced IRR. IRRs are frequently observed for mAb therapeutics with and without glyco-engineering, with, for example, an incidence of up to 77% for rituximab (chimeric antibody), a mAb targeting CD20 (31). Similarly, with the afucosylated mAb directed against CD20, obinutuzumab, IRRs were found to be the most frequently reported AEs, occurring in 86% of patients, and to be limited to grade 1 or 2 events (32). However, grade $\geq$3 events have been observed in one-fifth of patients in other obinutuzumab studies (33). Hence, the frequency and grading of IRRs after premedication for ARGX-110 proved to be mild and manageable (38.5% of patients and grade 1–2).

Among the patients who died due to SAE during the study, one was a CTCL patient who was admitted to the hospital with life-threatening sepsis due to multiple cutaneous barrier breaks localized on the tumor lesions. The patient died due to this event, considered not related to ARGX-110 by the investigator. In patients with advanced malignancies, infections are of concern and frequently occur, mainly because of bone marrow suppression and neutropenia from cytotoxic chemotherapies (34). The infectious complications of patients with CTCL are of importance since they are involved in over 50% of deaths in patients with CTCL (35–37).

Pharmacokinetic analyses of ARGX-110 demonstrated dose proportionality over the dose range of 1 to 10 mg/kg, but not at 0.1 mg/kg and a terminal half-life of 10 to 13 days. The measurement at day 7 (168 hours) was below LLOQ for the 0.1 mg/kg which may suggest that this dose shows an increased clearance which could be explained by target-mediated drug disposition as has been suggested for other antibodies at lower concentrations (32). Because of the limited number of patients and short observation window and no apparent correlations between pharmacokinetic parameters, and either clinical treatment response or adverse events, further investigations should be performed. Because 0.1 mg/kg did not show complete CDC, 10 mg/kg did not show better benefits than 5 mg/kg and to create a safety margin, the two intermediate doses 1 and 5 mg/kg, administered every 3 weeks, were chosen for future expansion cohorts including solid and hematologic malignancies.

Target modulation in circulating normal lymphocytes and tumor cells were followed by measuring CD70 mRNA levels using qPCR and the number of T, B, NK, and Treg cells were measured by flow cytometry. It was not possible to measure CD70 by flow cytometry after the first dose of ARGX-110 so the expression levels of CD70 on these cells could not be assessed. There was an overall tendency for decreased CD70 mRNA levels after treatment compared to predose, but no major changes in the numbers after ARGX-110 treatment in the overall patient population could be observed as measured by flow cytometry, but individual patients showed some effects. We cannot draw any conclusions from these data, but need to further explore the effects of ARGX-110 on subtypes of lymphocytes that could express CD70 as well as the expression of CD70 on tumor cells in the circulation.

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In vitro studies have shown that ARGX-110 binds with high affinity to different CD70$^+$ cell lines, inhibiting release of IL8 as a consequence of interfering with the NF-κB pathway and blocking Treg proliferation and activation (23). Inhibition is dose dependent and at picomolar concentrations. The ADCC potency of ARGX-110 was found to be increased >20-fold compared with the fucosylated form of the antibody, whereas CDC and ADCP function remained unimpaired when tested with solid and

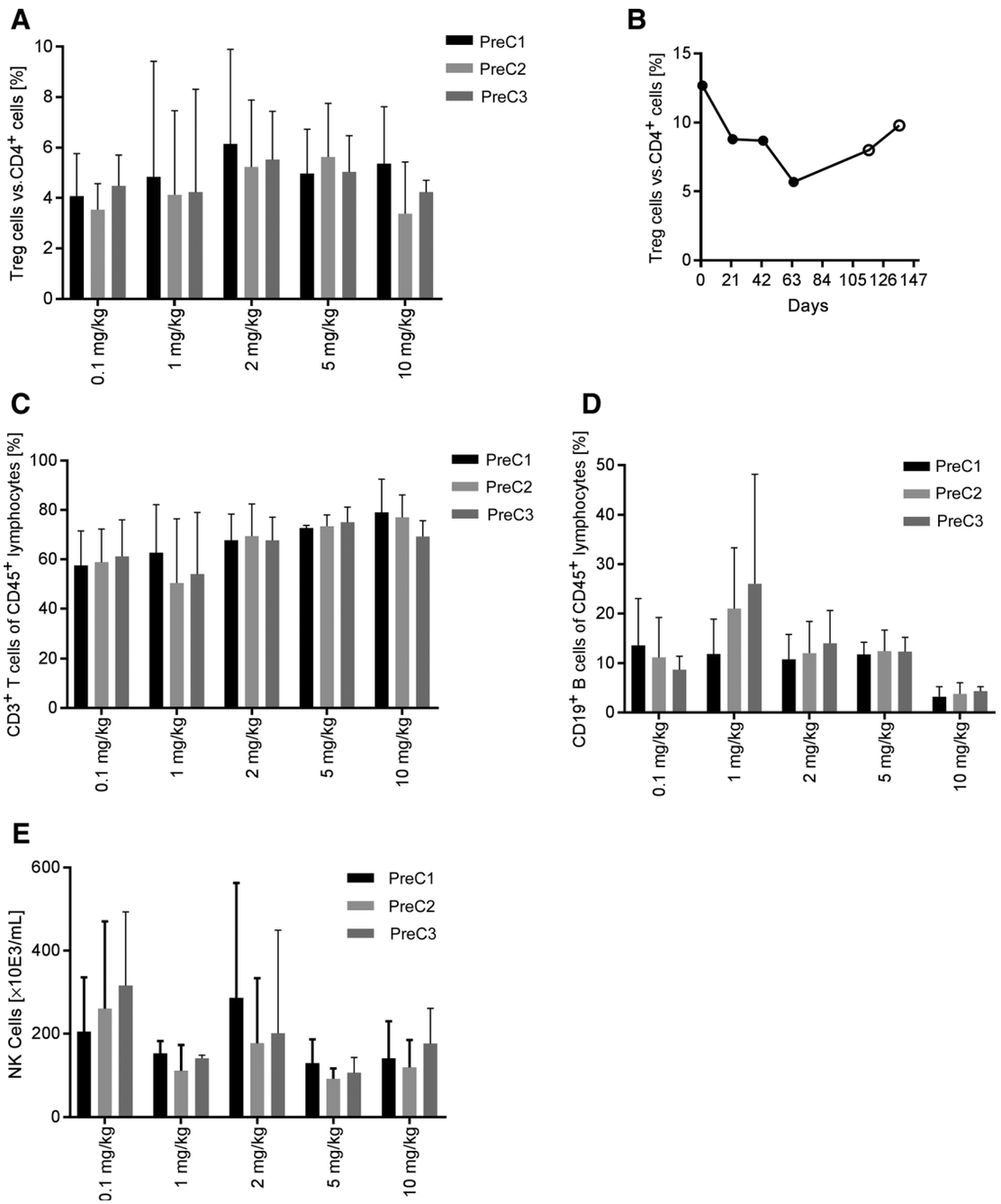

Figure 3.

Flow cytometry of lymphocytes in peripheral blood. **A,** Regulatory T cells (Treg) in whole blood (CD45, CD4, CD25, CD127, CD27 and the intracellular Foxp3) versus CD4$^+$ cells measured in whole blood. Mean and standard deviation (SD) of pre-C1–C3 as representative measurements when ≥50% of patients received treatment at doses 0.1, 1, 2, 5, and 10 mg/kg. **B,** Treg in a Hodgkin Lymphoma patient at 1 mg/kg measured pretreatment C1–C4 (black circles) and FU30 and FU60 (open circles). **C,** Flow cytometry of T cells in whole blood, detected by CD3 and measured as percentage (%) CD3$^+$ T cells of CD45$^+$ lymphocytes. Mean and SD of pre-C1–C3 samples at doses 0.1, 1, 2, 5, and 10 mg/kg. **D,** Flow cytometry of B-cells in whole blood detected by CD19 and measured as percentage (%) CD19$^+$ B cells of CD45$^+$ lymphocytes. Mean and SD of pre-C1–C3 samples at doses 0.1, 1, 2, 5, and 10 mg/kg. **E,** NK cells (CD45$^+$CD3$^-$CD16$^+$CD56$^+$ lymphocytes) were counted using flow cytometry in peripheral blood samples for each dose level (0.1, 1, 2, 5, and 10 mg/kg). Mean and SD.

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hematologic tumor cell lines (23). In the CTCL patient of the cohort treated with the highest dose of 10 mg/kg, a rapid and effective depletion of $CD70^+$ cells was achieved as judged on the results of the CD70 qPCR analysis. This patient was suffering from Sézary syndrome, which is characterized by large numbers of circulating malignant cells. The patient had the highest qPCR signal (approximately 31 vs. 3 as found in healthy individuals), which decreased by 77% after two administration cycles. IHC of the skin biopsies revealed strong CD70 and CD27 positivity (data not shown), therefore it is very likely that the circulating malignant clone was target positive explaining the high qPCR signal prior to treatment (unfortunately no FACS analysis was performed on blood cells). These data suggest an effective depletion of the Sézary cells, possibly due to enhanced ADCC in combination with CDC and ADCP.

In the other CTCL patient, the circulating clone could not be detected after four treatment cycles with 0.1 mg/kg ARGX-110, resulting in a complete response in the blood compartment. This patient also had strong CD70 and CD27 expression as shown by IHC. For AML, CLL, WM, and other B-cell malignancies, the coexpression of CD70 with its receptor CD27 on the tumor cells was described and *in vitro* studies with primary cells derived from ALL patients suggests the existence of an autocrine loop involved in proliferation of the tumor cells (10, 13, 22, 38). This has not been investigated for T-cell malignancies, so at this moment it is not known whether blocking the CD70–CD27 signaling pathway contributed to the reduction of circulating tumor cells in the two CTCL patients or if it was due to ADCC or other mechanisms of action.

Data suggest that CD70 plays a role in tumor evasion of host immune surveillance by promoting activation (39), proliferation, and survival of Treg cells in tumors, thereby encouraging tumor growth (20, 40). Potentially, by blocking CD70–CD27 signaling, recruitment/activation of Treg cells within the tumor microenvironment and CD70–CD27-activated growth signals could be inhibited. An indication for this inhibitory effect on Treg proliferation was obtained in the HL patient. The Reed–Sternberg cell has the highest CD70 expression as compared to other B-cell malignancies, whereas at least in Hodgkin's disease derived cell lines no coexpression of CD27 can be witnessed (41). Our immunohistology data confirm CD70 expression and the absence of CD27 for this patient (data not shown). Marshall and colleagues demonstrated for this indication the inhibitory activity of Tregs infiltrating the tumor thereby revealing their role in creating an immunosuppressive environment (42). Higher numbers of peripheral Tregs have been reported for HL (43, 44) as we have observed for the HL patient, who was treated with ARGX-110. After a few treatment cycles the number of Tregs declined steadily to almost the levels found in healthy individuals, suggesting that blocking CD70 indeed affects their proliferation. When treatment was discontinued, Treg numbers increased again, possibly because of relief of CD70 blockade. A similar observation was made for the AML patient, where also increased numbers of regulatory T cells have been reported (45).

The findings of this dose-escalation phase I trial provide evidence of good tolerability of ARGX-110 and preliminary antitumor activity at all dose levels in generally heavily pretreated patients with advanced CD70-positive malignancies, warranting further investigation in a safety expansion study. In summary, the MTD of ARGX-110 was not reached in the dose-escalation part of this study. Based on CDC data indicating an effective dose at 1 mg/kg and over and to further explore the dose–response relationship, to create a safety margin and to cover PK variability, 1 and 5 mg/kg will be further investigated in safety expansion cohorts including CD70 positive hematologic malignancies and solid tumors to see which population will benefit.

Disclosure of Potential Conflicts of Interest

P. Aftimos is a consultant/advisory board member for Synthon. L. van Rompaey, A. Hultberg, D. Gandini, H. De Haard, N. Leupin and A. Thibault hold ownership interest (including patents) in argenx. J. Michot is a consultant/advisory board member for Bristol-Myers Squibb. K. Silence is a consultant/advisory board member for SIVA. V. Ribrag is a consultant/advisory board member for Bristol-Myers Squibb, Epizyme, MSD, Roche, and SERVIER. No potential conflicts of interest were disclosed by the other authors.

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Clinical Cancer Research

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